International Vaccine Technology Workshop

Evaluating Vaccine Technology Options for Developing Countries

The Baculovirus - Insect Cell Expression System for Efficient Vaccine Production

Manon M.J. Cox

September 17, 2010

Protein Sciences CORPORATION

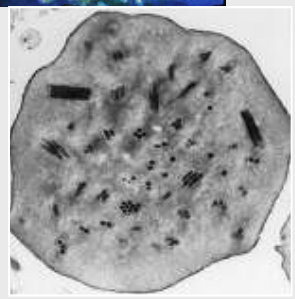
Vaccination Achievements

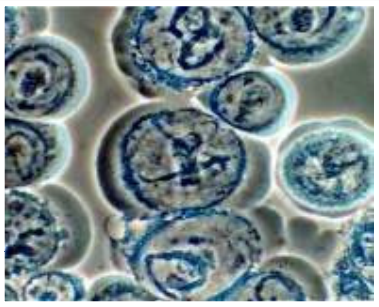
- Eradication of smallpox
- Elimination of polio in the Americas
- Control of pertussis, diphtheria, tetanus, measles, mumps, rubella
- New vaccines - blockbusters
  - Hepatitis A and B
  - Prevnar
  - Varicella (shingles)
  - HPV

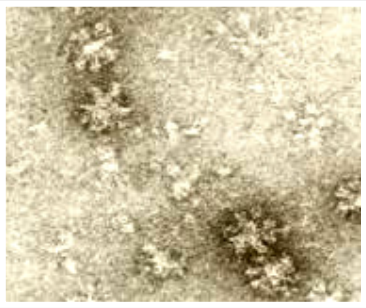
BEVS Technology

"Enabling products where speed, cost and safety matter"

Baculovirus Expression Vector System (BEVS)







- Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)
- Baculoviruses highly specific to insect cells
- Powerful promoter generates high yield of protein of interest

- Culture expression of insect cells in a fermenter
- Infect cells with engineered virus
- Incubate infection for ~48 - 72 hours

- Protein forms rosettes
- Purify protein to > 90% into final product
- Formulate with PBS into vaccine

FluBlok® Approval → Validation

BEVS Technology

"Enabling products where speed, cost and safety matter"

Key Advantages of BEVS Technology

- Versatility
  - Produced > 1,000 proteins
- Speed
  - Single serum-free cell line for all products
  - Cloning in weeks vs. months
- Low cost
  - High yields in a low-cost proprietary media
  - High-density fermentation
- Safety
- Reliable scale-up
  - Current scale 500L; others up to 5,000L

Insect Cell-Produced Products & Regulatory Approval Status

Cervarix – First insect cell product licensed by FDA

- Papillomavirus vaccine
- Oct. 19, 2009 - Approved in U.S
- 2007 - Approved in EU & Australia

Provenge® - Prostate cancer treatment

- First cancer immunotherapy to be approved by the Agency
- Approved May 2010

- Impact
  - Removes a “barrier” of for insect cell-based production platform from regulatory viewpoint

Now Approved

Cervarix®

Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant

gsk GlaxoSmithKline

Dendreon

Insect Cell-Produced Products Approaching FDA Approval with PSC's Assistance

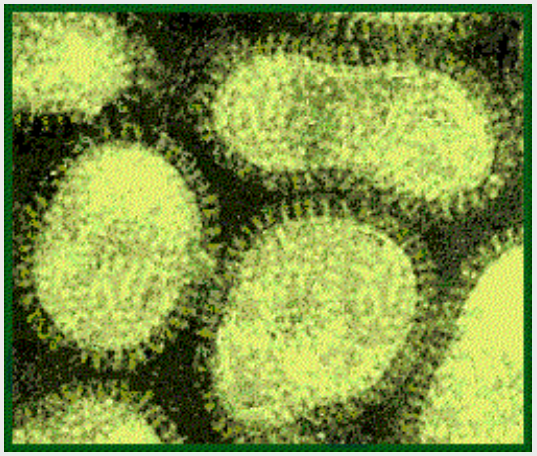
- **Glybera® - Lipoprotein Lipase Deficiency**
  - Recombinant Adeno-Associated Virus (rAAV) -based gene therapy
  - Orphan disease indication
  - BLA filed January11, 2010
- **Diamyd® – Type I Diabetes Vaccine**
  - Phase III studies ongoing in U.S. and Europe
  - Preservation of insulin secretion
  - Major partnership deal with J&J
- **FluBlok - Influenza Vaccine**
  - First non egg-based flu vaccine in U.S.
  - Under final review at FDA

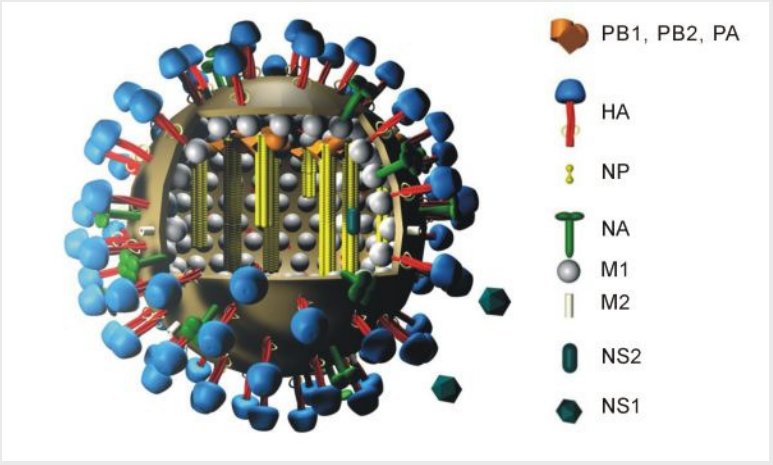
Examples of Vaccines that are being Produced in Insect Cells

- **Human therapeutic & prophylactic vaccines**
  - SARS – Spike – entering Phase I
  - HIV
  - Norovirus – Phase I
  - Hepatitis B, C and E
  - West Nile
  - Malaria
  - Dengue
  - Marburg, Ebola
- **Veterinary vaccines**
  - PCV
  - Influenza (avian; porcine; horse)

Influenza Vaccine: HA = Major Surface Protein

- **HA *(Hemagglutinin)*:**)
  - Coat of the influenza virus
  - Antibodies against HA protect against influenza
  - Changes in HA require annual update of vaccine





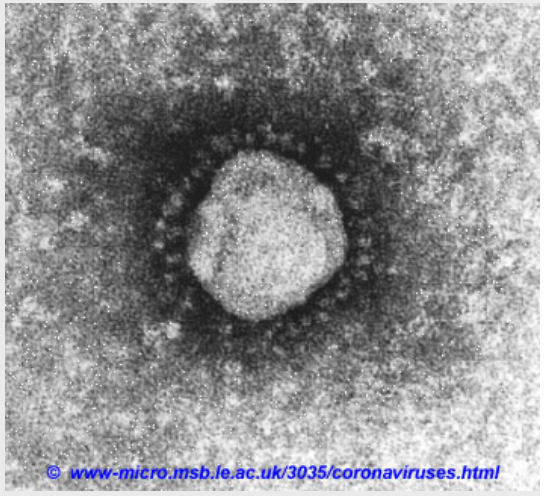
SARS Vaccine
S = Major Surface Antigen

Coronaviruses are large enveloped RNA viruses that infect mammals and birds

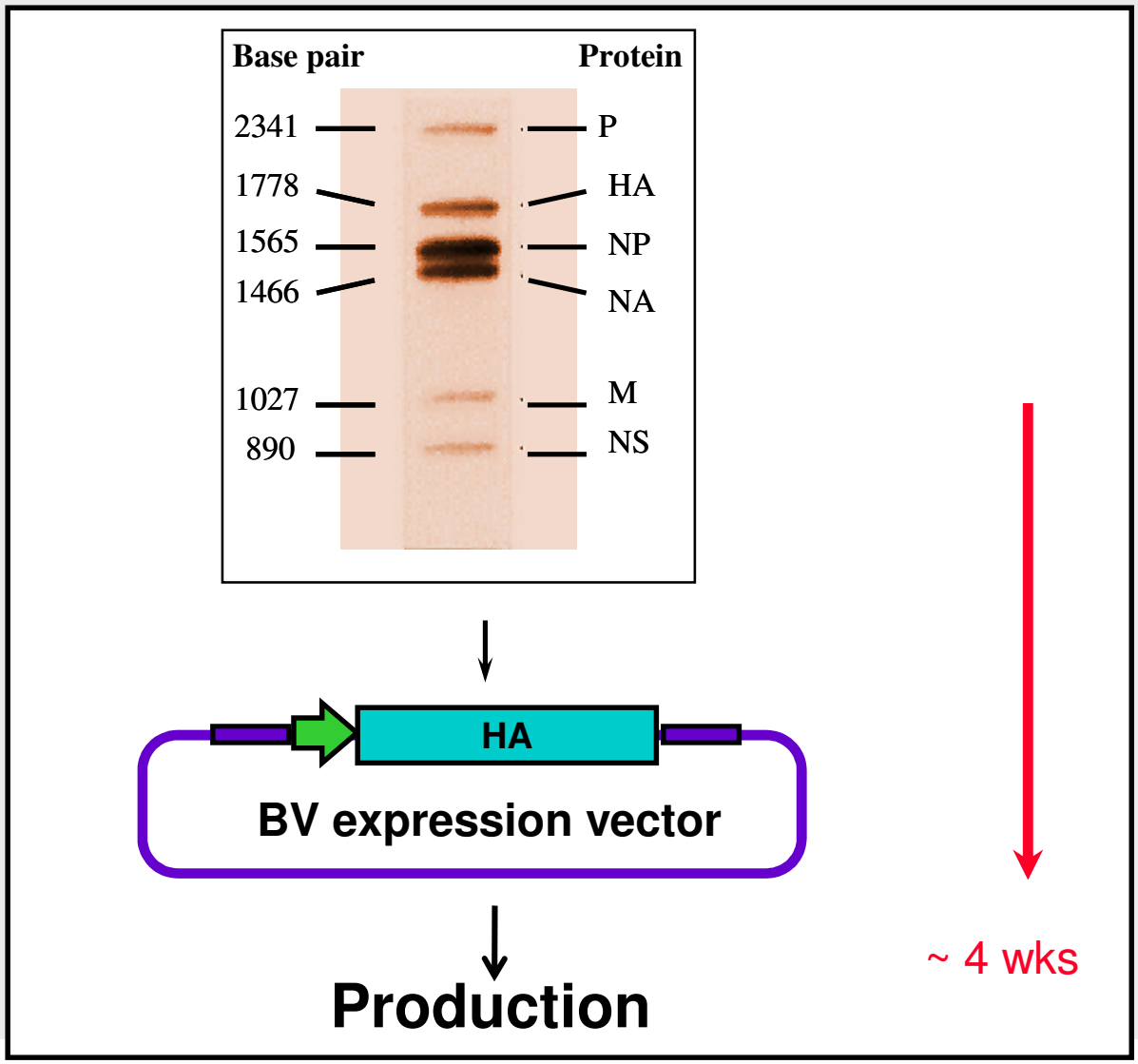
Target for vaccine: S - Spike glycoprotein (surface protein) = major antigen

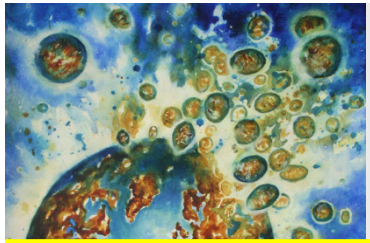
Rationale:

- Veterinary vaccine development
- Key to Infection - ACE2 receptor binding
- Antibodies to S-Protein identified from SARS survivors neutralized the virus

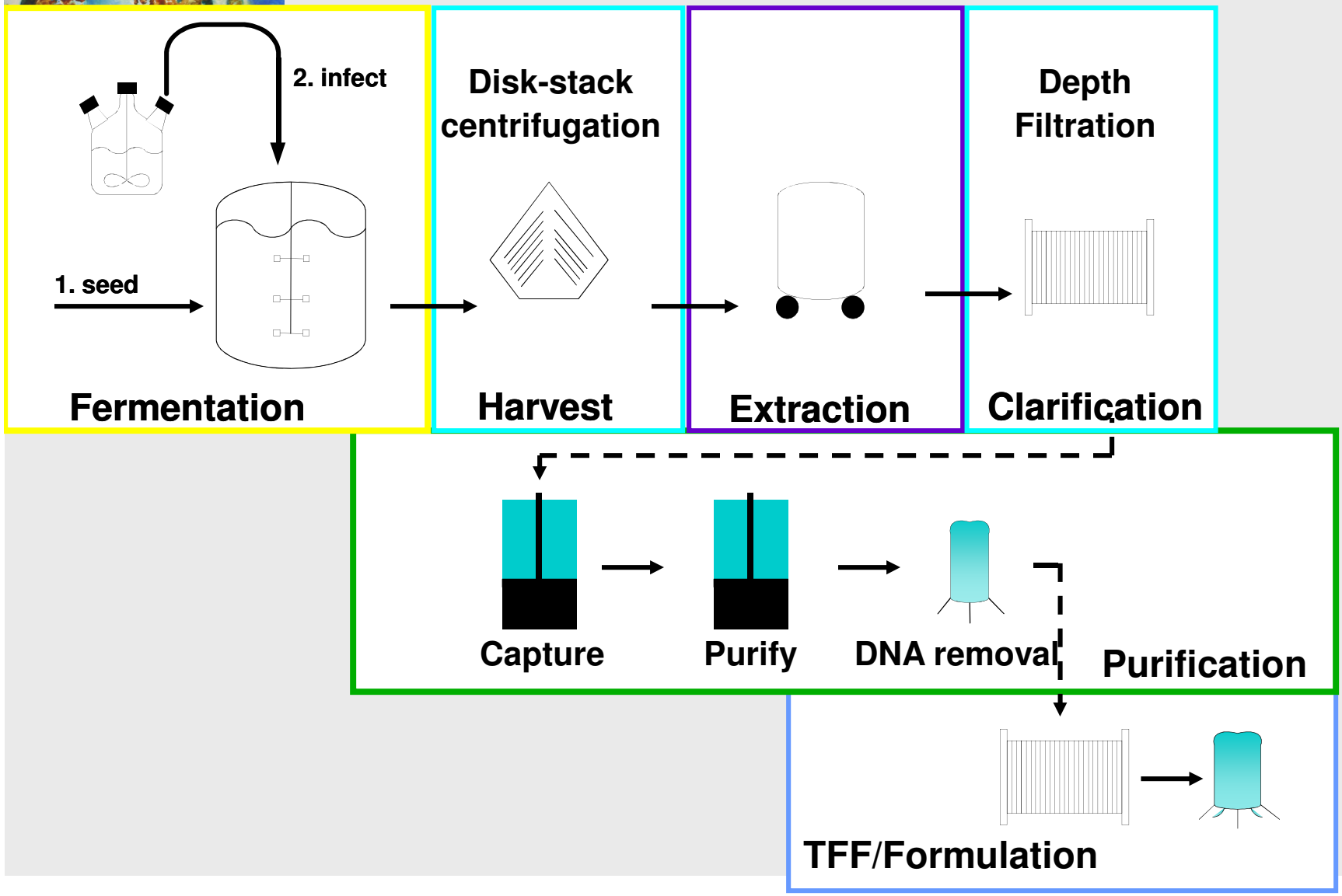


Cloning of Gene of Interest
Example: influenza HA

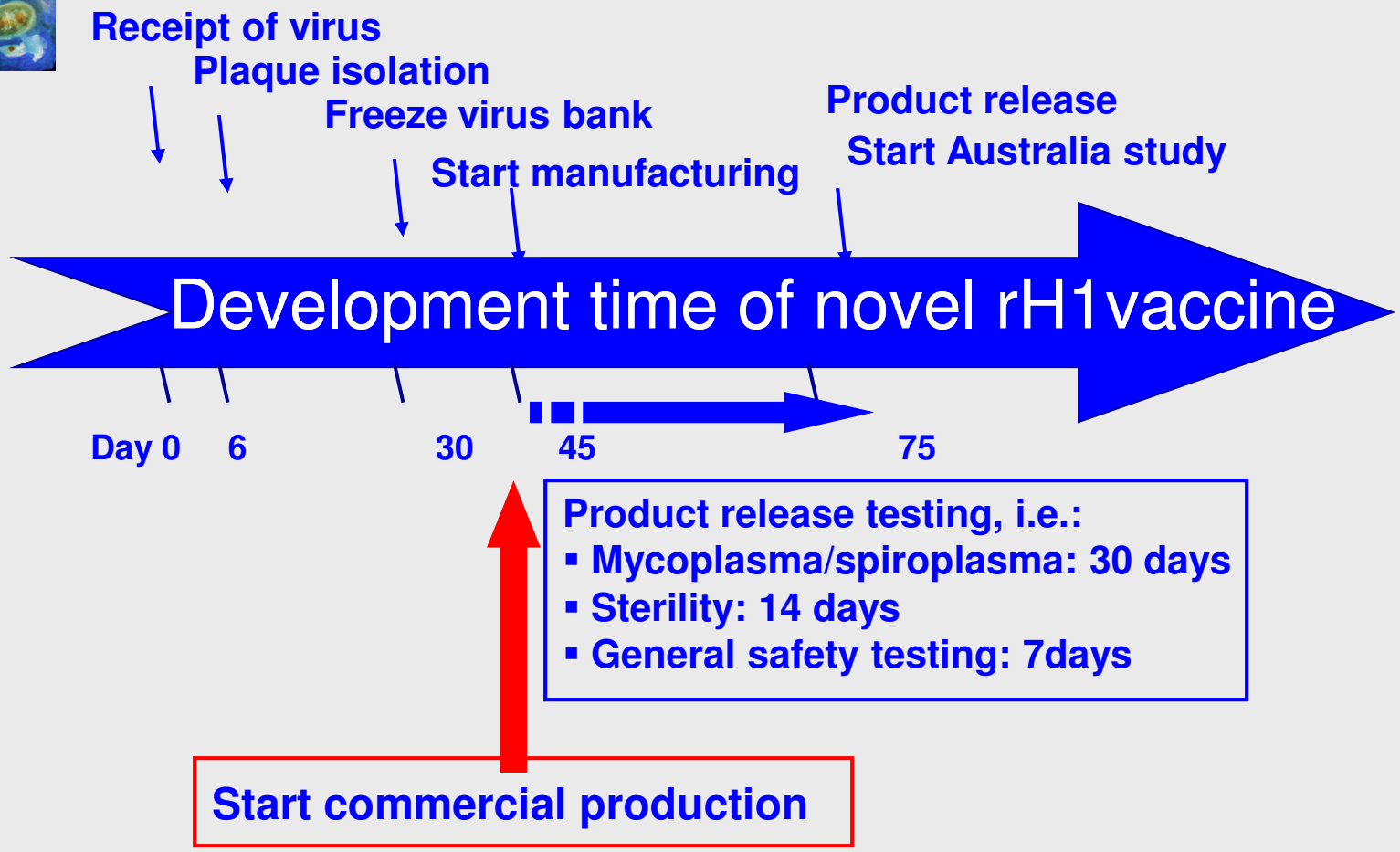




Schematic Production Process



Time-line for Vaccine Development
Novel rH1 Vaccine



Vaccine Production Capacity

Insect Cell culture
Baculovirus is added
↓
Centrifugation
***Pellet* is solubilized**
↓
Depth filtration
↓
Capture (IEX)
↓
Membrane Filtration
↓
Purification (HIC)
↓
Ultrafiltration
↓
Sterile Filtration

Mammalian Cell culture
↓
Centrifugation
***Supernatant* is processed**
↓
Depth filtration
↓
Capture
↓
(Membrane Filtration)
↓
Purification
↓
Ultrafiltration
↓
Sterile Filtration

- **Worldwide capacity for cell culture is 2.5 M L**
- **9M doses of 15µg/10,000L/5-days**
- **Billions of doses can be produced w.i. weeks**

Shortage of vaccine is unnecessary as there is adequate cell culture capacity available worldwide.

Conclusions

- The BEVS technology is a versatile rapid production technology to “tackle” emerging diseases of viral or parasitic origin (SARS, H5, Ebola)
- Safe vaccines can be produced fast & for low cost.
- Production facility can be multi-use to manufacture a broad range of products.
- No need to handle live dangerous viruses.
- Recent approval of BEVS derived products.
- Establishment of large scale manufacturing is high priority!